Amendments to the Specification

Please replace the paragraph at page 2, lines 6-12 with the following amended paragraph:

It has now been found that certain bis[thio-hydrazide amide] compounds are significantly cytotoxic to cancer cells, including cancer cells that have become multi-drug resistant. For example, Compound (1) had an IC_{50} of 0.005, 0.05 and 0.01 μM against the multi-drug resistant cell lines MES-SA/DX5, HL-60/TX1000 and Bowes/OV2, respectively (see Example 15). The IC_{50} for the anticancer drugs ~~taxol~~ Paclitaxel and vincristine was two to three orders of magnitude larger for the same cell lines (see Example 15). The structure of Compound (1) is shown below:

Please replace the paragraph at page 4, lines 13-19 with the following amended paragraph:

Another embodiment of the present invention is a method of treating a subject with cancer. The method comprising administering to the subject an effective amount of a compound represented by Structural Formula (I). The compound represented by Structural Formula (I) is administered as a monotherapy (i.e., as the only anti-cancer drug administered to the subject). Optionally a second anti-cancer agent is co-administered to the subject, provided that the second anti-cancer agent is other than ~~taxol~~ Paclitaxel or an analog of ~~taxol~~ Paclitaxel. When the subject is a mouse, then the compound is other than:

Please replace the paragraph at page 31, line 10 through page 33, line 4:

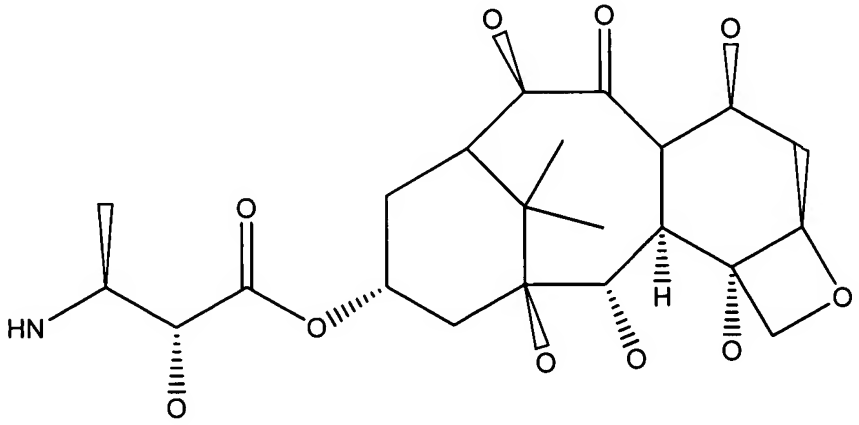
The compounds disclosed herein are believed to be particularly effective when co-administered with anti-cancer agents which act by arresting cells in the G2-M phases due to stabilized microtubules. Thus, the disclosed method preferably includes co-administered anti-cancer drugs which act by this mechanism. However, ~~taxol~~ Paclitaxel and analogs of ~~taxol~~ Paclitaxel are excluded from the present invention unless a multidrug resistant cancer is being treated. Examples of anti-cancer agents which act by arresting cells in the G2-M phases due to stabilized microtubules include without limitation the following marketed drugs and drugs in development: Erbulozole (also known as R-55104), Dolastatin 10 (also known as DLS-10 and NSC-376128), Mivobulin isethionate (also known as CI-980), Vincristine, NSC-639829,

Discodermolide (also known as NVP-XX-A-296), ABT-751 (Abbott, also known as E-7010), Altorhyrtins (such as Altorhyrtin A and Altorhyrtin C), Spongistatins (such as Spongistatin 1, Spongistatin 2, Spongistatin 3, Spongistatin 4, Spongistatin 5, Spongistatin 6, Spongistatin 7, Spongistatin 8, and Spongistatin 9), Cemadotin hydrochloride (also known as LU-103793 and NSC-D-669356), Epothilones (such as Epothilone A, Epothilone B, Epothilone C (also known as desoxyepothilone A or dEpoA), Epothilone D (also referred to as KOS-862, dEpoB, and desoxyepothilone B), Epothilone E, Epothilone F, Epothilone B N-oxide, Epothilone A N-oxide, 16-aza-epothilone B, 21-aminoepothilone B (also known as BMS-310705), 21-hydroxyepothilone D (also known as Desoxyepothilone F and dEpoF), 26-fluoroepothilone), Auristatin PE (also known as NSC-654663), Soblidotin (also known as TZT-1027), LS-4559-P (Pharmacia, also known as LS-4577), LS-4578 (Pharmacia, also known as LS-477-P), LS-4477 (Pharmacia), LS-4559 (Pharmacia), RPR-112378 (Aventis), Vincristine sulfate, DZ-3358 (Daiichi), FR-182877 (Fujisawa, also known as WS-9885B), GS-164 (Takeda), GS-198 (Takeda), KAR-2 (Hungarian Academy of Sciences), BSF-223651 (BASF, also known as ILX-651 and LU-223651), SAH-49960 (Lilly/Novartis), SDZ-268970 (Lilly/Novartis), AM-97 (Armad/Kyowa Hakko), AM-132 (Armad), AM-138 (Armad/Kyowa Hakko), IDN-5005 (Indena), Cryptophycin 52 (also known as LY-355703), AC-7739 (Ajinomoto, also known as AVE-8063A and CS-39.HCl), AC-7700 (Ajinomoto, also known as AVE-8062, AVE-8062A, CS-39-L-Ser.HCl, and RPR-258062A), Vitilevuamide, Tubulysin A, Canadensol, Centaureidin (also known as NSC-106969), T-138067 (Tularik, also known as T-67, TL-138067 and TI-138067), COBRA-1 (Parker Hughes Institute, also known as DDE-261 and WHI-261), H10 (Kansas State University), H16 (Kansas State University), Oncocidin A1 (also known as BTO-956 and DIME), DDE-313 (Parker Hughes Institute), Fijianolide B, Laulimalide, SPA-2 (Parker Hughes Institute), SPA-1 (Parker Hughes Institute, also known as SPIKET-P), 3-IAABU (Cytoskeleton/Mt. Sinai School of Medicine, also known as MF-569), Narcosine (also known as NSC-5366), Nascapine, D-24851 (Asta Medica), A-105972 (Abbott), Hemiasterlin, 3-BAABU (Cytoskeleton/Mt. Sinai School of Medicine, also known as MF-191), TMPN (Arizona State University), Vanadocene acetylacetonate, T-138026 (Tularik), Monsatrol, Inanocine (also known as NSC-698666), 3-IAABE (Cytoskeleton/Mt. Sinai School of Medicine), A-204197 (Abbott), T-607 (Tularik, also known as T-900607), RPR-115781 (Aventis), Eleutherobins (such as

Desmethyleleutherobin, Desaetyleleutherobin, Isoeleutherobin A, and Z-Eleutherobin), Caribaeoside, Caribaeolin, Halichondrin B, D-64131 (Asta Medica), D-68144 (Asta Medica), Diazonamide A, A-293620 (Abbott), NPI-2350 (Nereus), Taccalonolide A, TUB-245 (Aventis), A-259754 (Abbott), Diozostatin, (-)-Phenylahistin (also known as NSCL-96F037), D-68838 (Asta Medica), D-68836 (Asta Medica), Myoseverin B, D-43411 (Zentaris, also known as D-81862), A-289099 (Abbott), A-318315 (Abbott), HTI-286 (also known as SPA-110, trifluoroacetate salt) (Wyeth), D-82317 (Zentaris), D-82318 (Zentaris), SC-12983 (NCI), Resverastatin phosphate sodium, BPR-0Y-007 (National Health Research Institutes), and SSR-250411 (Sanofi).

Please replace the paragraph at page 33, lines 5 through page 34, line 8 with the following amended paragraph:

~~Taxol~~Paclitaxel, also referred to as ~~"Paclitaxel"~~ "TAXOL", is a well-known anti-cancer drug which acts by inhibiting microtubule formation. Many analogs of ~~taxol~~ paclitaxel are known, including ~~taxotere~~ docetaxol, which is also referred to as ~~""Docetaxol"~~ "TAXOTERE". Other ~~taxol~~ paclitaxel analogs are disclosed in the co-pending U.S. Serial Nos. 10/193,075 and 10/193,639, both entitled TAXOL ENHANCER COMPOUNDS and both filed July 10, 2002, the entire teachings of which are incorporated herein by reference. A "~~taxol~~ paclitaxel analog" is defined herein to mean a compound which has the basic taxane skeleton and the ability to arrest cells in the G2-M phases due to stabilized microtubules. The basic taxane skeleton is shown below in Structural Formula (VII):



(VII).

Double bonds have been omitted from the cyclohexane rings in the taxane skeleton represented by Structural Formula (VII). It is to be understood that the basic taxane skeleton can include zero or one double bond in one or both cyclohexane rings. In addition, a wide variety of substituents can decorate the taxane skeleton without adversely affecting biological activity. A number of atoms have also omitted from Structural Formula (VII) to indicate sites in which structural variation commonly occurs among ~~taxol~~ paclitaxel analogs. For example, substitution on the taxane skeleton with simply an oxygen atom indicates that hydroxyl, acyl, alkoxy or other oxygen-bearing substituent is commonly found at the site. It is to be understood that these and other substitutions on the taxane skeleton can also be made without losing the ability to enhance and stabilize microtubule formation.

Please replace the paragraph at page 80, lines 7-12 with the following amended paragraph:

HL-60, a model of myeloid leukemia, was obtained from ATCC (ATCC CCL-240); and HL60/TX1000 was isolated *in vitro* by subculturing HL-60 in progressively higher concentration of ~~Taxol~~ paclitaxel. HL-60/TX1000 cells over-express mdr-1 mRNA and p-glycoprotein (PCP), as determined by western blot and immunofluorescence labeling with antiPGP antibodies. The cells are cross-resistant to ~~Taxol~~ paclitaxel, Vincristine, Adriamycin, Etoposide and Doxorubicin.

Please replace the paragraph at page 80, line12 through page 81, line 1 with the following amended paragraph:

MES-SA, a model of uterine sarcoma, is sensitive to a number of chemotherapeutic agents, including Doxorubicin, Dactinomycin, Mitomycin C, ~~Taxol~~ paclitaxel and Bleomycin, but resistant to Vinblastine and Cisplatin. MES-SA /DX5 was established in the presence of increasing concentrations of Doxorubicin. The cells express high levels of mdr-1 mRNA and p-glycoprotein and exhibit cross resistance to more than fifteen chemotherapeutic agents including ~~Taxol~~ paclitaxel, Etoposide, Mitomycin C, Colchicine, Vinblastine, Dactinomycin, 5-Fluorouracil, Methotrexate and others. Both MES-SA and MES-SA/Dx5 were purchased from ATCC (ATCC CRL-1976 and ATCC CRL-1977, respectively).

Please replace the paragraph at page 81, lines 10-17 with the following amended paragraph:

A stock solution of Compound (1), ~~Taxol~~ paclitaxel (positive control) and Vincristine (positive control) were prepared by dissolving the compound at a concentration of 1 mM in 100% DMSO. Final concentrations were obtained by diluting the stock solution directly into the tissue culture medium. Cells were incubated with varying concentrations of compounds for 72 hours and the IC_{50} was determined by MTS (i.e. 3-(4.5-dimethylthiazol-2-yl)-2.5-diphenyl tetrazolium bromide) assay. The IC_{50} is the concentration of compound required to inhibit 50% tumor cell growth. The results are shown in Table 1.

Please replace Table 1 bridging page 81 and page 82 with the following amended Table 1:

Table 1 - Inhibition of Growth of Multi-Drug Resistant Tumor Cell Lines by Anti-Cancer Agents and Compound (**1**)

	IC_{50} (uM)					
	MES-SA	**MES-SA/DX5**	HL-60	**HL-60/TX1000**	Bowes	**Bowes/OV2**
~~Taxol~~ Paclitaxel	0.005	**5**	0.002	**5**	0.005	**5**
Vincristine	0.004	**5**	0.002	**5**	0.002	**5**
Compound (1)	0.05	**0.005**	0.4	**0.05**	0.2	**0.01**

Please replace the paragraph at page 82, lines 7-14 with the following amended paragraph:

As can be seen from the data in Table 1, ~~Taxol~~ paclitaxel and Vincristine demonstrated significantly high anti-cancer activity (IC_{50}: 0.002-0.005 uM) agaist normal cancer cell lines (MES-SA, HL-60, Bowes). However, these anti-cancer drugs were significantly less effective (IC_{50}: 5 uM) against the MDR cell lines (MES-SA/DX5, HL-60/TX1000, Bowes/OV2). On the

other hand, Compound (1) surprisingly showed higher anti-cancer activity against all three MDR cell lines. The specificity were 10 (= 0.05/0.005), 8 (=0.4/0.05), and 20 (=0.2/0.01) against MES-SA/DX5, HL60/TX1000, and Bowes/OV2, respectively.

Please replace Table 2 on page 83 with the following amended Table 2:

Table 2 - Inhibition of Growth of the Multi-Drug Resistant Tumor Cell Line MES-SA/DX5 by Compounds (2)-(18).

Compound	IC_{50} (uM) MES/DX5
~~Taxol~~ Paclitaxel	5
2	0.005
3	0.05
4	0.005
5	0.05
6	0.005
7	0.01
8	0.005
9	0.005
10	0.005
11	0.005
12	0.005
13	0.05
14	0.01
15	0.005
16	0.05
17	0.005
18	0.01

Please replace the paragraph at page 83, line 25 through page 84, line 2 with the following amended paragraph:

As can be seen from the data in Table 2, Compounds (2)-(18) demonstrated significant anti-cancer activity (IC_{50}: 0.05-0.005 uM) against the multi-drug resistant (MDR) cell line MES-SA/DX5, while ~~Taxol~~ paclitaxel showed very week anti-cancer activity (IC_{50}: 5 uM) against the same MDR cell line.

Please replace the paragraph at page 92, line 20 through page 93, line 2 with the following amended paragraph:

Compound (1) was prepared by dissolving the compound at a concentration of 10 mM in 100% DMSO. Final concentrations 10, 1, 0.1, 0.01 and 0.001 μM were obtained by diluting the stock solution directly into the tissue culture medium. Cells were incubated with varying concentrations of compounds for 72 hours and the IC50 was determined by MTS (i.e. 3-(4.5.-dimethylthiazol-2-yl)-2.5-diphenyl tetrazolium bromide) assay. IC50 is the concentration of compound required to inhibit 50% tumor cell growth. Table 3 shows the *in vitro* IC50 (ÿM) cytotoxicity results of Compound (1) versus vincristin and ~~taxol~~ paclitaxel.